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An Investigation Into Polyiodination of Activated Benzene Derivatives with Electrophilic Aromatic Substitution Reactions

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AN INVESTIGATION INTO POLYIODINATION OF ACTIVATED BENZENE DERIVATIVES WITH ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

by
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ABSTRACT

The aim of this research is to investigate the periodination of benzene derivatives that are activated towards electrophilic aromatic substitution. In this research, a successful electrophilic aromatic substitution reaction was completed with procedures that used iodine with silver sulfate as an activating agent in the reaction mixture. The ball-milling technique with N-iodosuccinnimide as the iodinating reagent was also explored. Only one iodine was added onto 4-iodoanisole as the activated benzene derivative. When 2,4-dichloroanisole was the substrate, a small amount of diiodo product accompanied the monoiodo product, but no triiodo (periodinated) product was observed. Nonetheless, the trials of this research give valuable insight into extensions of previously published works that will not facilitate the polyiodination of activated benzene derivatives.

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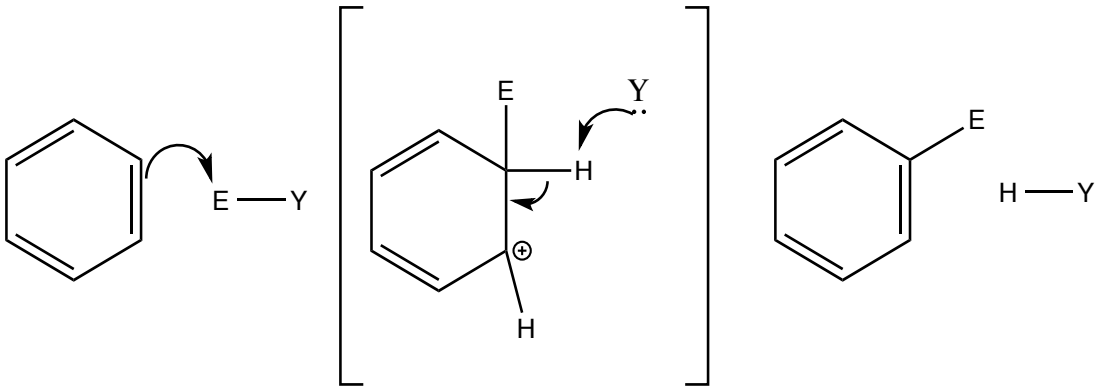
Introduction.

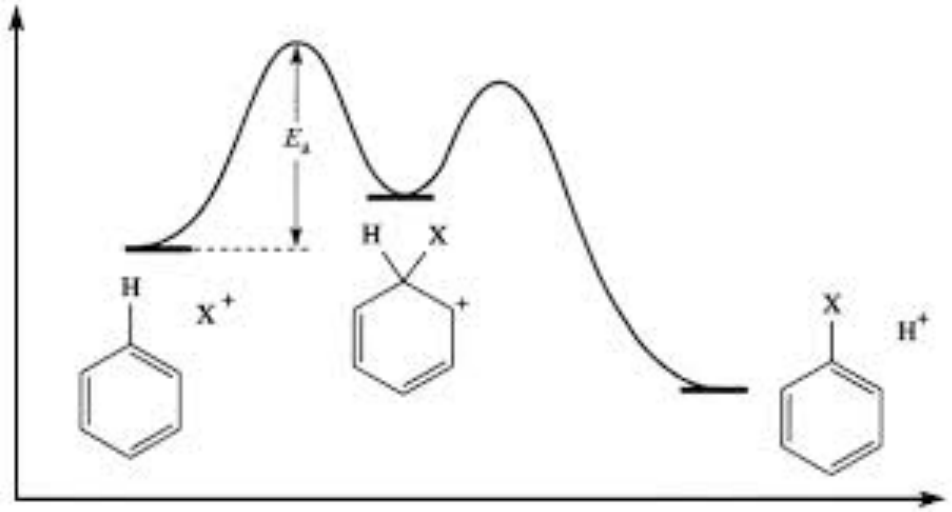
Electrophilic aromatic substitution reactions are organic reactions that substitute an electrophile for a hydrogen on an aromatic ring. An electrophile, a species that is electron loving and usually cationic, will react with an aromatic system in electrophilic aromatic substitution reactions that occur in two steps. The first step in the mechanism is to create a carbocation, specifically an arenium ion, by way of a pair of electrons from the aromatic ring pi system attacking an electrophile. The second step consists of a Lewis base donating electrons to the hydrogen at the point of substitution on the unstable carbocation, which allows that hydrogen to leave its electrons behind, for the carbocation to lose its charge, and for the system to restore aromaticity.



The rate-determining step in electrophilic aromatic substitution reactions is normally the first step, as the benzene derivative must lose its aromaticity and become a less-stable carbocation, both of which entail increases in free energy. For this reason, a very strong electrophile is needed for the electron rich aromatic ring

to attack in order to form the carbocation. The energy diagram for an electrophilic aromatic substitution reaction can be seen below.

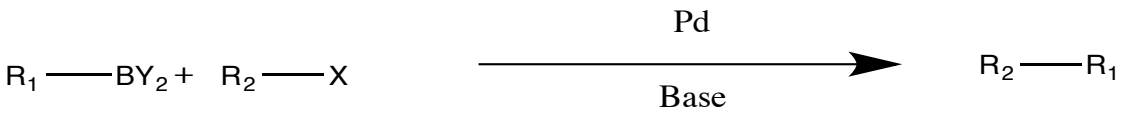
A common type of electrophilic aromatic substitution reaction is a halogen substitution reaction. In electrophilic halogenations with chlorine or bromine, creating a strong electrophile is achieved by reacting chlorine or bromine with iron or aluminum to create ferric bromide, ferric chloride, aluminum bromide or aluminum chloride, respectively. These Lewis acid catalysts can then react with the remaining bromine or chlorine to form highly polar complexes that serve as strong electrophiles in electrophilic halogenation reactions.



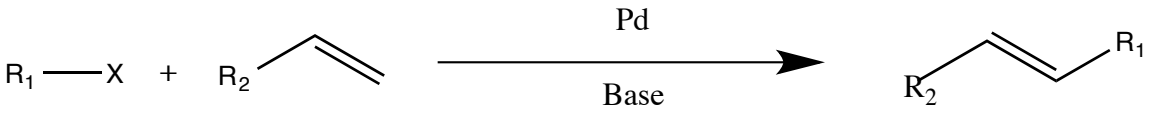
Electrophilic iodination reactions, however, do not proceed as other electrophilic aromatic substitution halogenation reactions do. Iodinations are more difficult to achieve because iodine, unlike bromine and chlorine, does not give a negative overall reaction enthalpy in electrophilic aromatic substitution reactions. For iodine to work, an additional oxidant such as periodic acid must be present.

With this in mind, iodinations of benzene or of benzene derivatives is an area of interest and research, as iodobenzene derivatives are useful in organic synthesis in reactions such as the Suzuki, Heck, and Sonogashira reactions.

The Suzuki cross-coupling reaction is a use for the iodobenzene derivatives in organic synthesis because halogen substituents can be replaced with a new carbon carbon bond through the use of a boronic acid, a palladium catalyst, and a base.

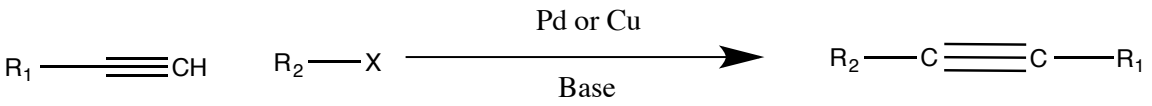


The Heck reaction is also a useful reaction with iodobenzene derivatives and very similar to the Suzuki reactions in the fact that a new carbon carbon bond is formed. This mechanism also calls for the use of a palladium catalyst and a base and differs from the Suzuki in that the other carbon in the new carbon carbon bond comes from an alkene.



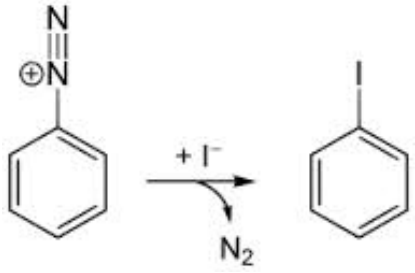
Finally, another use for iodobenzene derivatives in organic synthesis is through the Sonogashira reaction. Like the Suzuki reaction and the Heck reaction, the Sonogashira reaction also creates a new carbon carbon bond. However, with these reactions a terminal alkyne is needed; it will replace the halogen with a new carbon carbon triple bond. This reaction can lead to all of the I's on a polyiodinated

benzene being replaced and forming a highly branched target like spokes on a wheel.



R_1 = Aryl

At first, the premium method for introducing iodine into benzene derivatives included doing a diazotization on an amino benzene to create an arenediazonium ion, and then substituting iodine onto the arenediazonium using potassium iodide.



An alternative long process with low yields included mercuration followed by iododemercuration with triiodide anion. However, to avoid a tedious, dangerous, and inefficient process, the focus transitioned toward direct iodinations of benzene derivatives. Other oxidants that are known to allow direct iodination are oxidation reagents like nitric acid, iodic acids, sulfuric acid, sulfur trioxide, and hydrogen peroxide. These reagents generate a better electrophile out of molecular iodine.

For the research of this thesis, of interest is the creation of periodo benzene derivatives, benzene derivatives that have all positions not occupied by other groups substituted with iodine. The aim of this research is to investigate the periodination of benzene derivatives that are activated towards electrophilic aromatic substitution.

The first method that influenced this research comes from a paper published in 1983 by Dr. Mattern at The University of Mississippi. It[1] shows that the original speculation that a direct periodination procedure could not be efficient without displacing the other substituents was pessimistic, as the results indicate exhaustive periodination of deactivated and unactivated aromatic substrates. The method described in the paper called for a 3:1 ratio of I_2:H_5IO_6 in sulfuric acid at 100 °C for the periodination of benzene and unactivated benzene derivatives. The 3:1 ratio of I_2:H_5IO_6 in sulfuric acid at 100 °C is a mixture that can be viewed as equivalent to "I^+", thus creating the strong cationic electrophile for the electrophilic aromatic substitution reaction to take place. Below is the balanced chemical reaction that was just described.

$$1/7\ H_5IO_6 + 3/7\ I_2 + H+ \rightarrow I^+ + 6/7\ H_2O$$

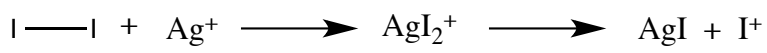
From this method the results show very high yields for periodination of the following: benzene, nitrobenzene, benzoic acid, chlorobenzene, phthalic anhydride, and toluene. Benzonitrile was converted to pentaiodobenzamide.[1] These are the first high yield successful periodination reactions.

The limitation of this method, however, is its inability to periodinate an *activated* aromatic ring, thus leaving an avenue that can be further investigated. This seems to be a conundrum because when one substitutes an activating group onto a benzene ring, it makes that benzene ring more reactive by way of electron donation by either electron induction or electron resonance. Such activated benzene derivatives should be more apt to react with the iodonium cation. However, this is not the case in this procedure because the activated rings apparently subject the

aromatic ring to destruction by the strongly acidic and oxidizing reaction conditions. Thanks to this publication several pieces of valuable insight were gained. First, is that periodination of benzene derivatives is a feasible task, and secondly that an additional avenue of investigation was available, as they were unsuccessful in periodinating activated benzene derivatives.

Unlike the 1983 publication, which focused on periodinating benzene derivatives, a publication by Joshi and co-workers focused on regioselectively iodinating aromatic compounds.[2] The attractiveness of this article, despite not periodinating aromatic compounds, is that they are able to directly iodinate activated benzene derivatives using several different silver salts and get very high yields of their desired products. Their goal was to regioselectively iodinate chlorinated aromatic compound for use as pharmaceuticals. They report that the iodoarene moiety is an important structural motif in certain biologically active molecules (e.g., thyroid hormone) and a synthetic intermediate for a variety of chemistry products, including radiopharmaceuticals, environmental contaminants, and numerous bioactive compounds. One example of a prescription drug synthesized from an iodoarene intermediate is galanthamine, an acetylcholinesterase inhibitor for the symptomatic treatment of senile dementia of Alzheimer patients.[2] They report successful electrophilic iodination of phenols, anisoles, and anilines, all of which are activated aromatic compounds, with a procedure that calls for adding 1 mmol of the benzene derivative to 3 mL of a stirred solvent containing 1 mmol of iodine and 1 mmol of the respective silver salt. From this method one can infer that the silver salt in solution is ionized into a silver cation

and an anion. The silver cation will react with the iodine in solution creating an electrophilic AgI_2^+ complex or AgI with an iodonium cation available for electrophilic aromatic substitution onto an aromatic compound.

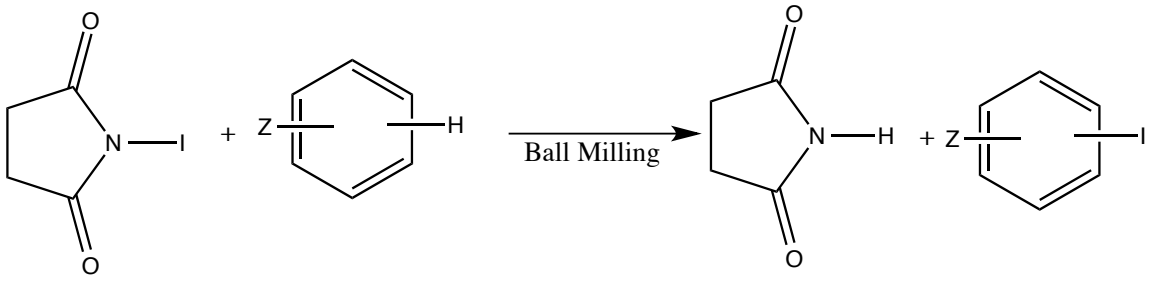


In this paper, the researchers only successfully added 1 or 2 iodines.[2] We proposed that it may be possible, if the reaction were pushed with heat and excess iodine and silver, to be able to *per*iodinate an activated benzene derivative. The pushing of these reactions is thus an area that can be further investigated to achieve periodination of activated aromatic compounds.

Similar to the previous publication, a publication by Schmidt, Stolle and Ondruschka displays an alternative way to directly halogenate aromatic compounds.[3] Their method describes a solvent-free procedure utilizing a ball mill machine. With a ball mill machine, the reagents are locked into a stainless steel capsule with stainless steel mill balls and violently shaken for a determined period of time to produce a product through the interactions created by the shaking and the mill balls. Their method calls for placing $KHSO_5$ (oxone) and NaX (X = Cl, Br) as the reagents into a ball mill with mixing auxiliary and milling balls, resulting in high levels of conversion of benzene derivatives to halogenated products.[3] Just like the previous publication, this is also a method that might be able to be pushed to periodinate aromatic compounds, although they only described chlorinations and brominations. Another valuable insight from this paper is the background knowledge about using the mixing ball mill machine. The paper outlines the number of ball mills, the auxiliary, the frequency, and the amount of reagent needed to

successfully run the ball mill machine.

A final publication by Bose and Mal contributed to the current research.[4] This paper uses the ball-milling process like the previous paper did, but it shows actual iodination reactions. This procedure calls for the use of N-iodosuccinimide in combination with a benzene derivative to complete the halogenation reaction.[4] Below is the hypothesized reaction. Like the procedure with the silver salts, the researchers once again did not push the reaction to its fullest extent, and is an area to be investigated.



By analyzing the previously mentioned publications while remaining focused on the goal of this research, to periodinate activated benzene derivatives, there appear several areas of interest that need to be investigated. The first experiment of the research included performing one of the same reactions as described in by Joshi et al.[2] except to run it with and without the silver salt to ensure that the silver salt is indeed required in order for the halogenation to proceed. Next, the same reactants, 2,4-dichloroanisole, silver sulfate, and iodine in n-hexane were once again reacted except that the reaction was pushed with excess silver salt and excess iodine to attempt to achieve a periodination of the 2,4-dichloroanisole. The third experiment

in the research was to use the same conditions and reactants as the previous experiment, but to use 4-iodoanisole. This experiment not only entailed pushing the reaction with excess silver salt and iodine like the previous experiment, but to also alter the solvent in an attempt to periodinate the 4-iodoanisole. The fourth part of the experiment entailed running the same reactions, but increasing the temperature by running them while they were heated under reflux. Finally, the last part of the experiment was done using the ball mill machine. Not only was the reaction with 4-iodoanisole, a silver salt, and iodine run, as in the Joshi experiments, but 4-iodoanisole was also run with N-iodosuccinimide as in the Bose and Mal paper.

Experimental Procedures.

Procedure for Iodination of Dichlorinated Anisole without Silver Salt

Iodine (1 mmol) was added into a stirred solution of 2,4-dichloroanisole (1 mmol) in hexane (3 mL). The reaction mixture was allowed to stir at room temperature for approximately 20 hours. The reaction mixture was placed in an ice bath to cool and quenched with a saturated aqueous solution of sodium metabisulfite (0.2 mL). The mixture was filtered through Celite in a crude filtration and the residue was washed with hexane (3**x**3 mL). The filtrate collected from the crude filtration was washed with aqueous sodium bicarbonate (3 mL), water (3 mL), and brine (3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed with the rotary evaporator. The remaining residue was then dissolved in deuterated chloroform and analyzed by proton NMR.

General Procedure for Iodination of Dichlorinated Anisole with Silver Salt

Silver sulfate (from 1 mmol to 4 mmol) and iodine in varying amounts (from 1 mmol to 4 mmol) were added into a stirred solution of 2,4-dichloroanisole (1 mmol) in hexane (3 mL). The reaction mixture was allowed to stir at room temperature for approximately 20 hours. The reaction mixture was placed in an ice bath to cool and quenched with a saturated aqueous solution of sodium metabisulfite (0.2 mL). The mixture was filtered through Celite in a crude filtration and the residue was washed with hexane (3**x**3 mL). The filtrate collected from the crude filtration was washed with aqueous sodium bicarbonate (3 mL), water (3 mL), and brine (3 mL). The combined organic phases were dried over Na_2SO_4 and the

solvent was removed with the rotary evaporator. The remaining residue was then dissolved in deuterated chloroform and analyzed by proton NMR.

General Procedure for Iodination of Anisole Derivative with Silver Salt

Silver sulfate (from 1 mmol to 4 mmol) and iodine in varying amounts (from 1 mmol to 4 mmol) were added into a stirred solution of 2,4-dichloroanisole (1 mmol) in varying solvents (3 mL). The reaction mixture was allowed to stir at room temperature for approximately 20 hours. The reaction mixture was placed in an ice bath to cool and quenched with a saturated aqueous solution of sodium metabisulfite (0.2 mL). The mixture was filtered through Celite in a crude filtration and the residue was washed with hexane (3**x**3 mL). The filtrate collected from the crude filtration was washed with aqueous sodium bicarbonate (3 mL), water (3 mL), and brine (3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed with the rotary evaporator. The remaining residue was then dissolved in deuterated chloroform and analyzed with a proton NMR.

General Procedure for Iodination of Iodoanisole with Silver Salt and heat

Silver sulfate (4 mmol) and iodine (4 mmol) were added into a stirred solution of 4-iodoanisole (1 mmol) in varying solvents (3 mL). The reaction mixture was heated under reflux for 24 hours. The reaction mixture was placed in an ice bath to cool and quenched with a saturated aqueous solution of sodium metabisulfite (0.2 mL). The mixture was filtered through Celite in a crude filtration and the residue was washed with hexane (3**x**3 mL). The filtrate collected from the

crude filtration was washed with aqueous sodium bicarbonate (3 mL), water (3 mL), and brine (3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed with the rotary evaporator. The remaining residue was then dissolved in deuterated chloroform and analyzed by proton NMR.

General Procedure for Iodination of Iodoanisole with Silver Salt in Mill Ball

Silver sulfate (from 1 mmol to 4 mmol) and iodine in varying amounts (from 1 mmol to 4 mmol) were added with 1 mmol of 4-iodoanisole and the 5 milling balls into the mill ball capsule. The capsule was closed and the reaction was allowed to run at 25 Hz for in varying time amounts from 1 hour to three hours. The residue was treated with n-hexane, to dissolve the all aromatics present; then the reaction mixture was placed in an ice bath to cool and quenched with a saturated aqueous solution of sodium metabisulfite (0.2 mL). The mixture was filtered through Celite in a crude filtration and the residue was washed with hexane (3**x**3 mL). The filtrate collected from the crude filtration was washed with aqueous sodium bicarbonate (3 mL), water (3 mL), and brine (3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed with the rotary evaporator. The remaining residue was then dissolved in deuterated chloroform and analyzed by proton NMR.

General Procedure for Iodination of Iodoanisole with NIS in Mill Ball

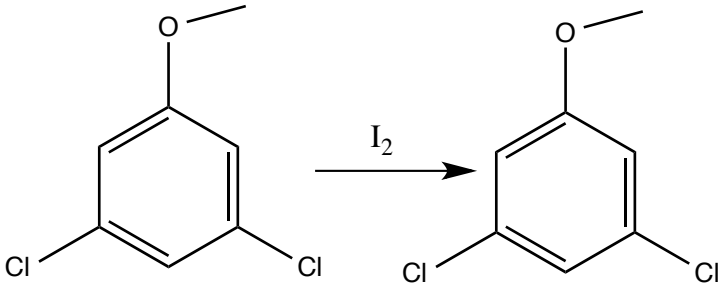
N-Iodosuccinimide (from 1 mmol to 4 mmol) was added with 1 mmol of 4-iodoanisole and the 5 milling balls into the mill ball capsule. The capsule was closed and the reaction was allowed to run at 25 Hz for in varying time amounts from 1

hour to three hours. The residue was treated with ethyl acetate. All precipitates were removed during a gravity filtration and the solvent was removed from the filtrate with the rotary evaporator. The precipitates from the gravity filtration were dissolved in DMSO and were subjected to an NMR. The remaining residue from the rotary evaporator was then dissolved in deuterated chloroform and analyzed by proton NMR.

Results and Discussion.

Iodination of Dichlorinated Anisole without Silver Salt

When dichloroanisole was treated with iodine in hexane as described above, no electrophilic aromatic substitution reaction took place. This conclusion can be made based on NMR analysis of both the starting material 2,4-dichloroanisole, and the residue that remained after the solvent was removed under reduced pressure. The NMR of pure 2,4-dichloroanisole yielded the following NMR shifts: ^{1}H (300 Hz, $CDCl_3$): δ/ppm 3.78 (s, 3H), 6.79 (d, 2H), 6.94 (s, 1H). The NMR of the reaction residue produced these exact same shifts.

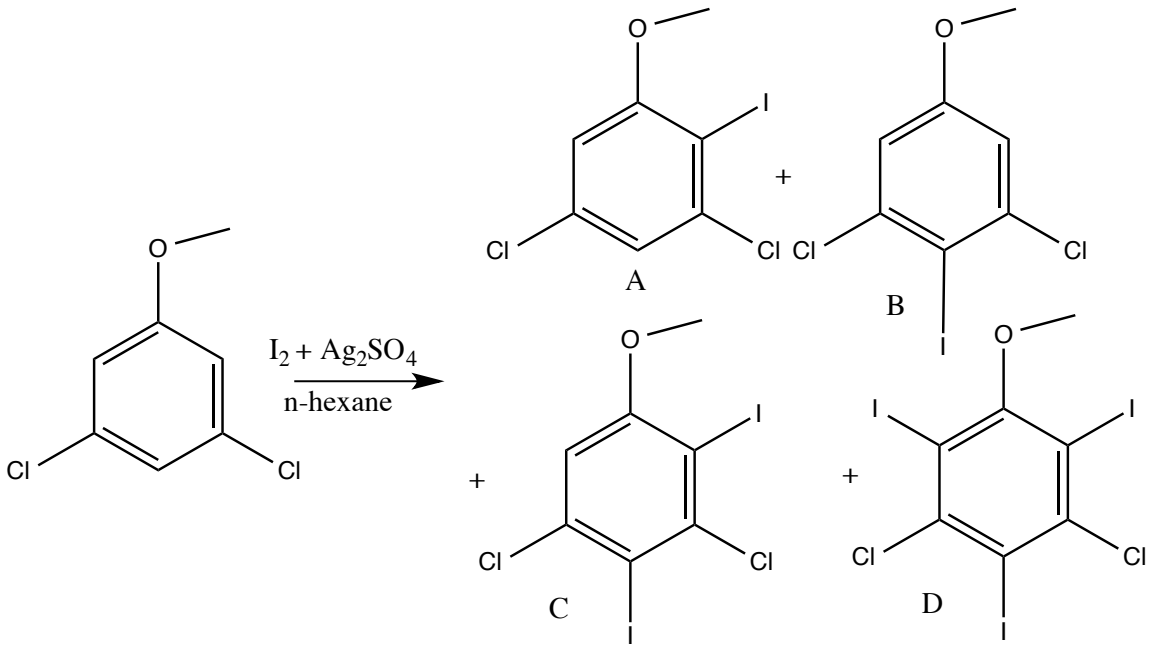


This reaction was used as a control reaction for the entire project. This reaction showed that the silver sulfate is in fact essential and must be present in order to be able to perform the desired Electrophilic Aromatic Substitution reaction to be able to substitute iodonium cations onto the benzene derivative.

Iodination of Dichlorinated Anisole with Silver Salt

The first reaction run under these particular conditions was run along with the previous section's reaction, but with 1 mmol of both silver sulfate and iodine.

The NMR analysis after the workup this time did in fact produce an NMR that showed an electrophilic reaction occurred, as there was a new methyl peak and new signals in the aromatic region of the NMR. This confirmed that the silver salt is essential.



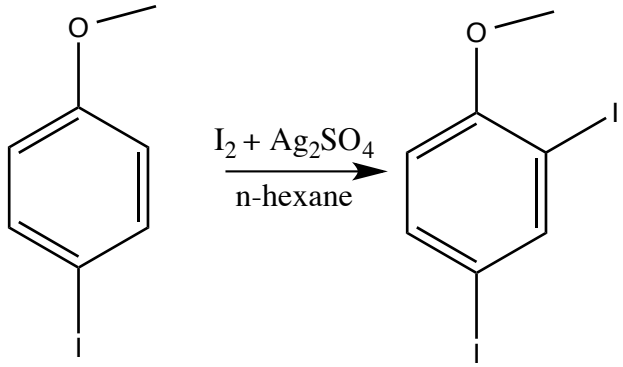
Due the goal of the project being to periodinate activated benzene derivatives, the reaction was then pushed by using 4 equivalents of both iodine and silver sulfate. This produced the results in the following figure and the following NMR data: ^1H (300 Hz, $CDCl_3$): δ/ppm 3.78 (s, 0.84H), 3.88 (s, 3H), 6.67 (s, 0.7H), 6.79 (s, 0.21H), 6.84 (s, 0.26H), 6.94 (s, 0.37H), and 7.12 (s, 0.72H). Based on integration and the known shift of the products it can be inferred that 8.69% was remaining starting material, there was a 58.8% conversion to product A, a 12% conversion to product B, and a 20.50% conversion to product C. Compared to the literature, these results had a lower total conversion percentage, as they reported 100% conversion. Their percent conversions to the different products reported were 28%, 48%,

and 11% when they only used one mmol of iodine and silver sulfate.[2] Even though a tri-iodo product, Product D above, was not synthesized, these results played an important role in the project as they showed the halogenation reactions could be pushed. That is, using 4 equivalents of iodinating reagents produced a greater amount of the diiodo-substituted product than reported in the literature. The increase was a small one, however, and it is not clear why our conditions produced a 7:1 ratio of A:B, while the literature conditions gave an A:B ratio of 1:1.7.

Going forward, the percent conversions may increase by applying heat or even a combination of heat and pressure in an autoclave, but because the iodination of the chlorinated derivative was not part of the project goal, this was not completed and the focus became the iodination of anisole.

Iodination of Iodoanisole with Silver Salt

The first iodination reaction run using silver sulfate as a catalyst was in n-hexane. The procedure was performed under the same conditions that the iodination reactions of the chlorinated benzene derivative were run under except that the staring material was 4-iodoanisole. 4-Iodoanisole was chosen because 4 is the logical first substitution position of anisole, due to the methoxy being an ortho/para director and the steric hindrance of the methoxy group for its ortho position. N-hexane was chosen as solvent because it showed the shortest reaction time in the Joshi et al. paper.



The NMR analysis from this reaction revealed that with n-hexane as the solvent, the product formed was 2,4-diiodoanisole. This was the product whether one mmol of iodine and silver sulfate was used or if they were used in excess.

This result led to the belief that in order to create a strong enough electrophile in solution to induce the second electrophilic aromatic halogenation, more silver cations must be in solution. A solubility test was done in order to determine what silver sulfate's solubility was in various other solvents. Ag_2SO_4 was most soluble in acetic acid and ethanol. In theory these polar solvent should induce the ionization of the Ag_2SO_4, thus increasing the number of silver ions in solution that could associate with the iodine to create a stronger electrophile for the electrophilic aromatic substitution reaction. It is unclear why hexane was the best solvent in the literature description, since little silver sulfate is expected to be soluble in hexane.

The results from running the reactions with the previously mentioned solvents are in the table below.

Starting Material	Solvent	Time (Hours)	Silver Salt Amount (mmol)	Iodine Amount (mmol)	Product
4-Iodoanisole	Ethanol	16	1	1	2,4-diiodoanisole
4-Iodoanisole	Acetic Acid	16	1	1	2,4-diiodoanisole
4-IodoAnisole	Ethanol	24	4	4	2,4-diiodoanisole
4-IodoAnisole	Acetic Acid	24	4	4	2,4-diiodoanisole

2,4-Diiodoanisole was deemed the product in the reactions, as they all had the following chemical shifts: ^{1}H (300 Hz, $CDCl_3$): δ/ppm 3.8(s, ~3H), 6.85 (d, ~1H), 7.68 (d, ~1H), and 8.01 (s, ~1H).

It can be seen from the table that changing the solvent and increasing the amount of reagents did not induce a second electrophilic aromatic halogenation reaction to occur. The results from these reactions were quite surprising, as one would believe that the addition of the second and third iodine to the ring would not be a problem at the 2 and 6 positions on the aromatic ring, both or which are activated by the methoxy group. Some explanations into why the substitution incorporating the third iodine may have been a problem would be that the third iodination at the 6 position incorporates steric strain since three large groups are placed next to each other; or that the silver ions are simply not electrophilic enough to induce the electrophilic aromatic substitution once the aromatic ring has been deactivated with two iodines.

Going forward with this research, it would be appropriate to try the reactions with a less sterically hindered activated benzene derivative such as phenol. Another valuable alteration would be to use a silver salt that, when in solution, could

produce a stronger base to help facilitate the second step of the electrophilic aromatic substitution reaction.

Iodination of Iodoanisole with Silver Salt and heat

The iodination reactions with ethanol, acetic acid or 4-butanol as solvent were all run while being heated under reflux for approximately 24 hours. The ethanol and the acetic acid were used as controls to see if heat would push the reactions. Butanol was used to see if the reaction would proceed better at a higher temperature as butanol has a higher boiling point. The results from these reactions are in the table below.

Starting Material	Solvent	Time (Hours)	Silver Salt Amount (mmol)	Iodine Amount (mmol)	Product
4-Iodoanisole	Ethanol	24	4	4	2,4-diiodoanisole
4-Iodoanisole	Acetic Acid	24	4	4	2,4-diiodoanisole
4-Iodoanisole	4-butanol	24	4	4	2,4-diiodoanisole

These products were once again characterized by NMR data that consisted of: : ^{1}H (300 Hz, $CDCl_3$): δ/ppm 3.8(s, ~3H), 6.85 (d, ~1H), 7.68 (d, ~1H), and 8.01 (s, ~1H).

From these results it is clear that heat does not influence these particular electrophilic aromatic substitution reactions, and with future research, time would be better spent altering other variables within the reactions.

Iodination of Iodoanisole with Silver Salt in the Ball Mill

Due to perceived solubility problems with the silver sulfate and the iodine going into solution together, the electrophilic aromatic substitution reaction was run in a machine that can perform these reactions without a solvent, the Ball Mill Machine. In the ball mill machine only 60% of the starting material when pushed with excess iodine and silver salt was converted into product. Based on the NMR it was determined that the product that was created was once again 2,4-diiosoanisole, as characterized by the following NMR data: ^{1}H (300 Hz, $CDCl_3$): δ/ppm 3.8(s, ~3H), 6.85 (d, ~1H), 7.68 (d, ~1H), and 8.01 (s, ~1H). Even an excess of iodine and silver sulfate did not achieve conversions as complete as the solution-phase reactions described above.

Iodination of Iodoanisole with NIS in Ball Mill

Using 4-iodoanisole and N-iodosuccinimide in a ball mill machine, no reaction occurred with 1 or 4 mmol of the NIS. The ball mill machine can facilitate a reaction and then degrade the product if let run too long, but this was not the case as an NMR was taken after 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hours, 2 hours and 3 hours. The literature does not report this reaction, but does report it with methylated anisole. The increased activation by the methyl groups must play a role in these reactions. Going forward, it would be logical to try to push the reaction using a methylated activated benzene derivative.

Overall in this research, a successful electrophilic aromatic substitution reaction was completed with procedures that used silver sulfate as an oxidizing agent in the reaction mixture. Despite only adding one iodine onto an

activated benzene derivative, the trials of this research give valuable insight into extensions of previously published works that will not facilitate the polyiodination of activated benzene derivatives. Going forward with this research, it would be appropriate to try the reactions that involved silver sulfate with a less sterically hindered activated benzene derivative such as phenol, as well as to use a silver salt that, when in solution, could produce a stronger base to help facilitate the second step of the electrophilic aromatic substitution reaction. The final continuation of this research would be to further analyze iodination of more activated benzene derivatives in the mill ball machine.

References.

1. Mattern, D. *J. Org. Chem.* **1984**, *49*, 3051-3053. "Direct Aromatic Periodination"

2. Joshi, S.N; Vyas, S.M.; Wu, H.; Duffel, M.W.; Parkin, S.; Lehmler, H. *Tetrahedron.* **2011**, *67,* 7461-7469. "Regioselective iodination of chlorinated aromatic compounds using silver salts"

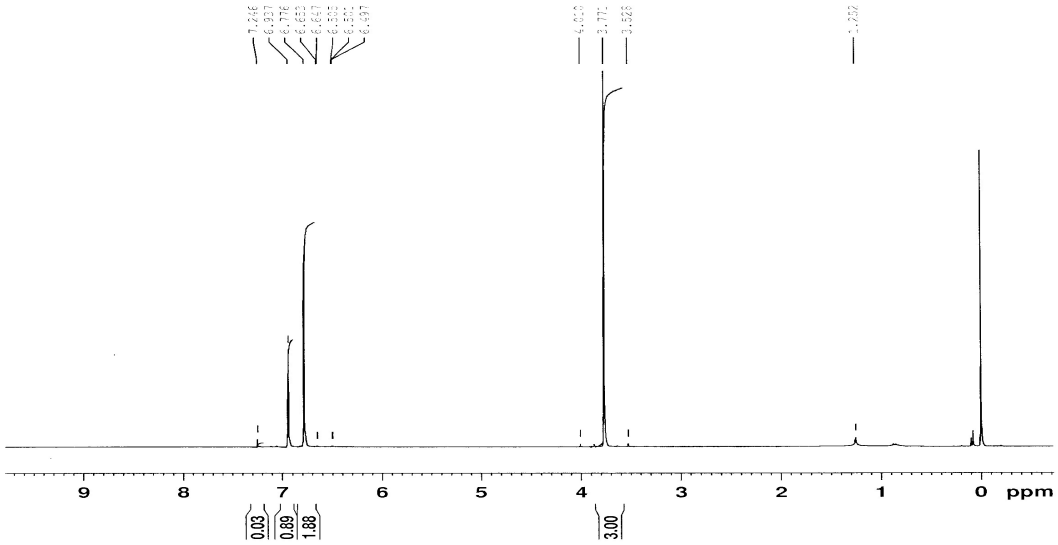
3. Schmidt, R.; Stolle, A.; Ondruschka, B. *Green Chem.* **2012**, *14,* 1673. "Aromatic substitution in ball mills: formation of aryl chlorides and bromides using potassium peroxomonosulfate and NaX**"**

4. Bose, A.; Mal, P.; *Tetrahedron Letters.* **2014,** *55,* 2154-2156. "Electrophilic aryl-halogenation using N-halosuccinimides under ball-milling"

Experimental Data.

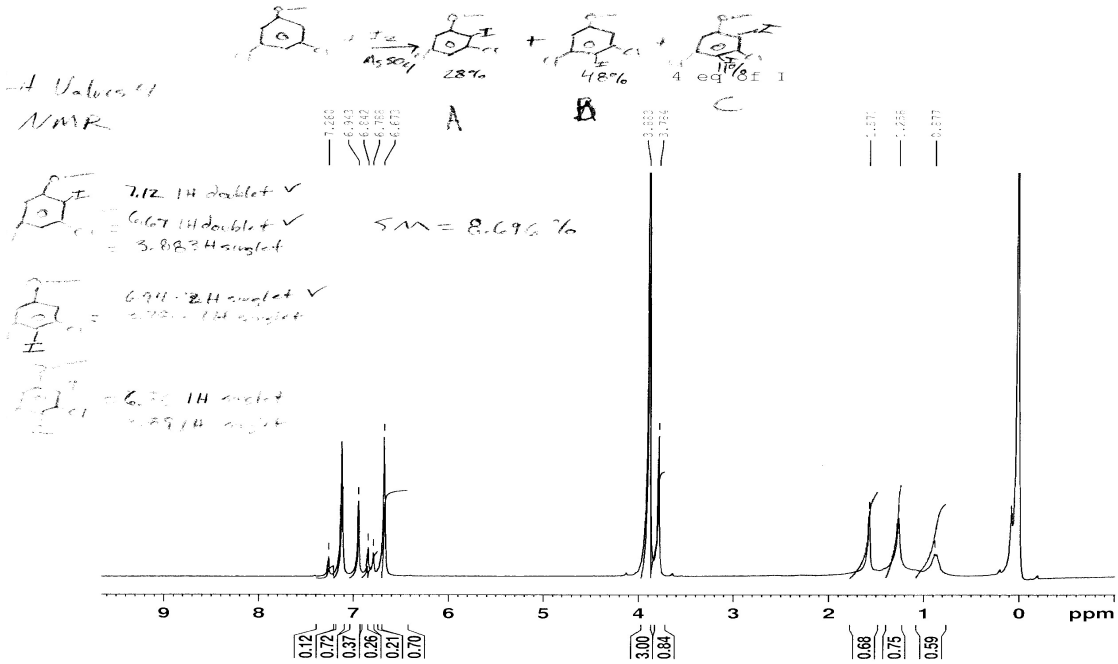
Iodination of Dichlorinated Anisole without Silver Salt

-Below is the NMR data from this reaction showing that no reaction took place as the NMR clearly indicates 100% of the starting material, 2,4-dichloroanisole.



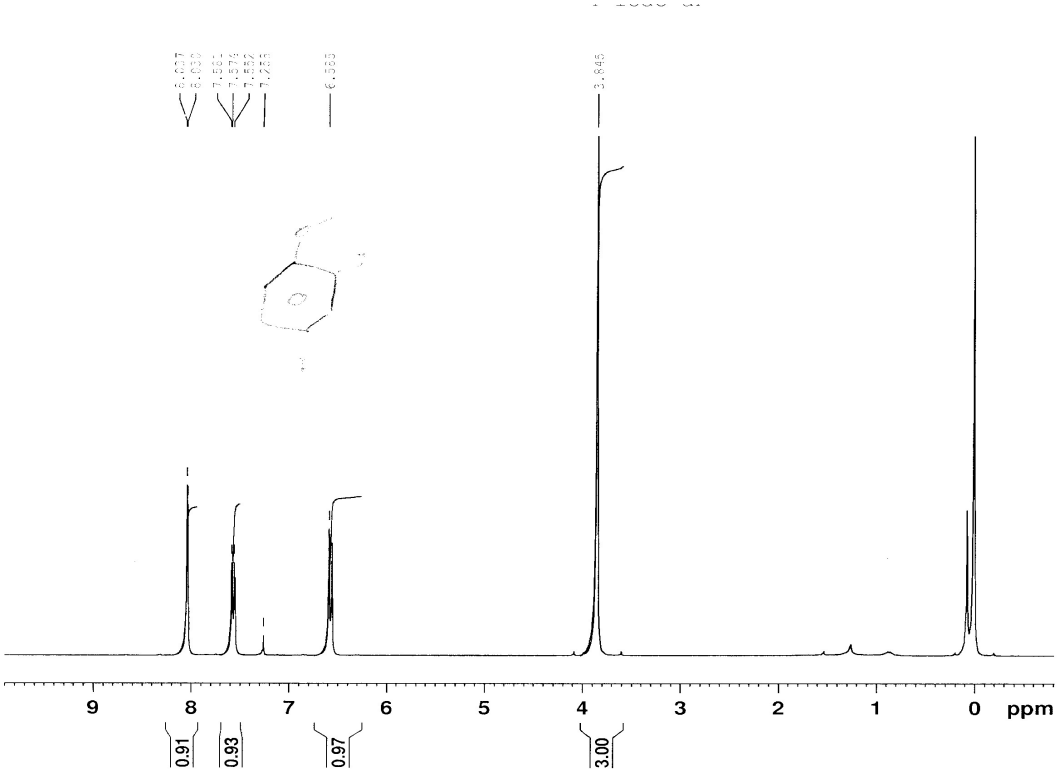
Iodination of Dichlorinated Anisole with Silver Salt

-Below is the NMR of this reaction with 4 equivalents of Iodine.

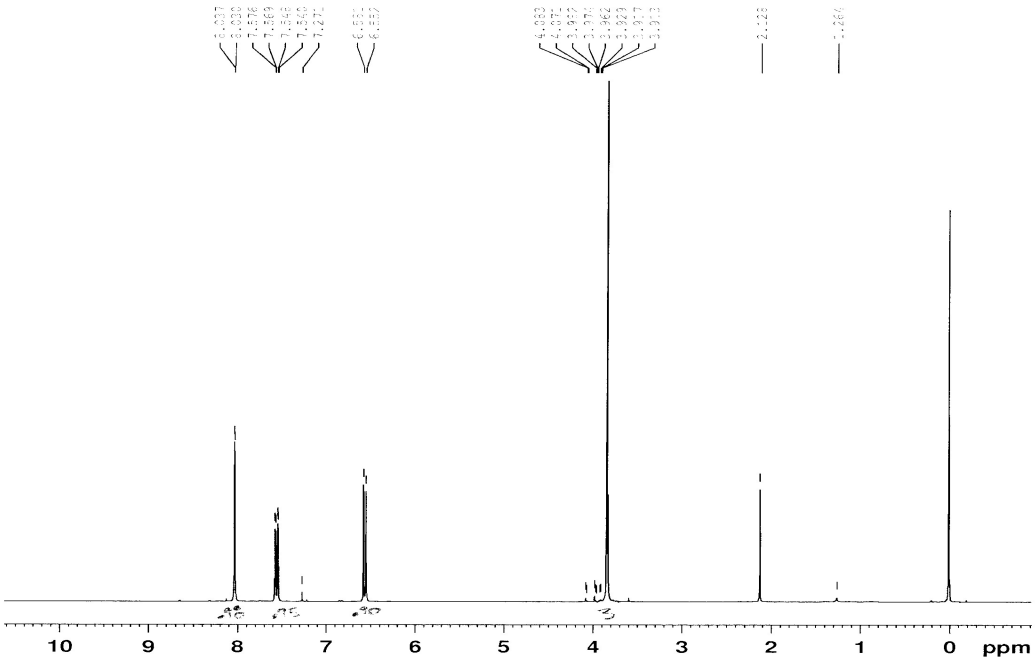


Iodination of Iodoanisole with Silver Salt

-Below is the results from reaction run in hexane. The product is 2,4-diiodoanisole.

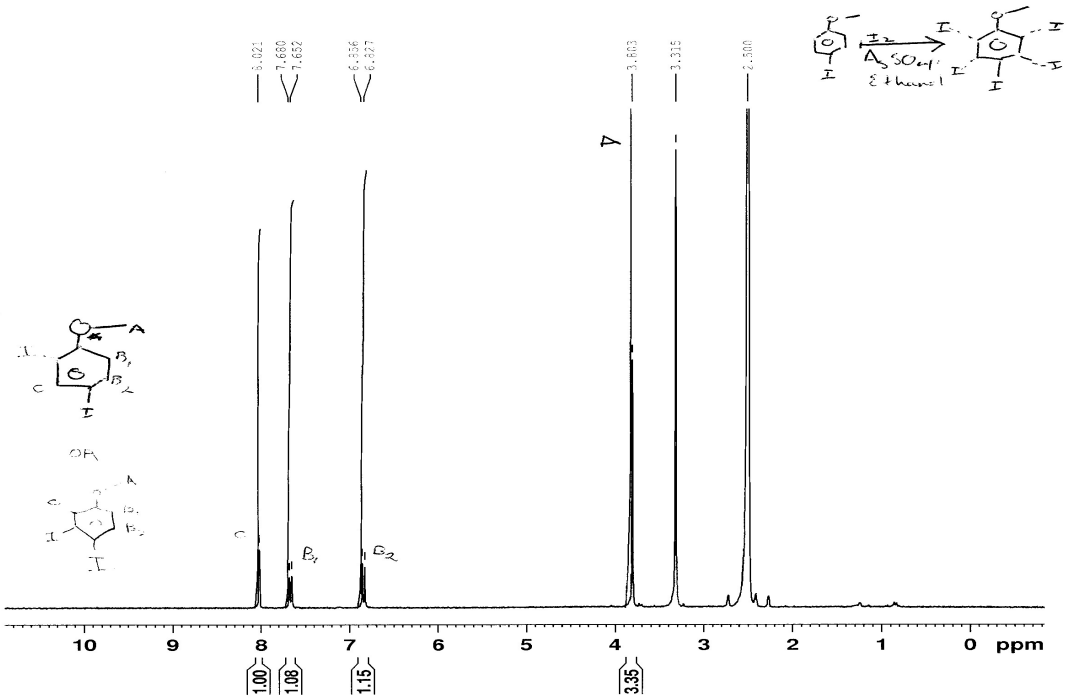


-Below is the results form the reaction run in acetic acid. The product is 2,4-diiodoanisole.



Iodination of Iodoanisole with Silver Salt and heat

- Below is the results form the reaction run in ethanol.



Iodination of Iodoanisole with Silver Salt in the Ball Mill

-Below is the NMR data from this reaction with 4 iodine and silver equivalents. The result indicates 40% starting material and 60% 2,4-diiodoanisole.